Type 2 Diabetes: A Systems Biology Approach

Network Medicine, Gene Expression, Drug-Target Landscapes, and Molecular Dynamics

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Abstract

We present a comprehensive computational analysis of Type 2 Diabetes (T2D) molecular mechanisms using four complementary approaches: (1) protein interaction network analysis of 13,715,404 human interactions from STRING v12.0, identifying a coherent T2D disease module (Z = 22.28, p < 10■■■); (2) gene expression meta-analysis across 4 pancreatic islet datasets (256 samples); (3) drug-target landscape of 3,552 compounds across 7 targets from ChEMBL, revealing 47 multi-target compounds; and (4) 100 ns molecular dynamics simulation of insulin lispro on Cornell BioHPC (48 cores, AMBER99SB-ILDN). IL6 emerges as the top hub (degree = 299), and CHEMBL509032 shows dual potency (INSR 20 nM + GCK 50 nM).

1. Introduction

Type 2 Diabetes affects 537 million people worldwide (IDF 2021) and costs $966 billion annually. Despite 400+ GWAS risk loci, translating genetics into therapeutics remains challenging because T2D is a systems disease involving insulin signaling, glucose metabolism, β-cell function, and chronic inflammation. Network medicine maps disease genes onto the human interactome to identify hubs, bridges, and disease modules — the same approach that identified baricitinib for COVID-19 (Gysi et al., PNAS 2021).

2. Data and Methods

2.1 Protein Interaction Network

STRING v12.0 human PPI: 13,715,404 edges. High-confidence (≥700): 473,860 edges, 16,201 nodes. 26 T2D seed genes from GWAS and literature spanning insulin signaling (INSR, IRS1, IRS2, AKT1, AKT2), β-cell function (INS, GCK, HNF4A, PDX1, KCNJ11), GLP-1 pathway (GLP1R, DPP4), metabolic sensors (PPARG, PRKAA1, SLC5A2), and inflammation (IL6, TNF, NFKB1).

2.2 Gene Expression

Four GEO datasets: GSE25724 (13 samples), GSE38642 (63 samples, Taneera et al. 2012), GSE41762 (77 samples, Fadista et al. PNAS 2014), GSE76894 (103 samples, Segerstolpe et al. Cell Metab 2016). Total: 256 human islet samples.

2.3 Drug-Target Landscape

ChEMBL bioactivity data for 7 targets: Insulin Receptor (CHEMBL1981), GLP-1R (CHEMBL4093), SGLT2 (CHEMBL3510), DPP-4 (CHEMBL284), PPARγ (CHEMBL235), AMPK (CHEMBL2842), Glucokinase (CHEMBL3983). Total: 3,552 unique compounds.

2.4 Molecular Dynamics

Insulin lispro monomer (PDB: 1MSO, 839 atoms) + 4,024 TIP3P waters + 2 Na■ = 12,911 atoms. AMBER99SB-ILDN force field. EM (1,115 steps), NVT (100 ps, 300K), NPT (100 ps, 1 bar), production MD

(100 ns). GROMACS 2022.1 on BioHPC cbsuecco12 (48 cores, ~195 ns/day).

3. Results

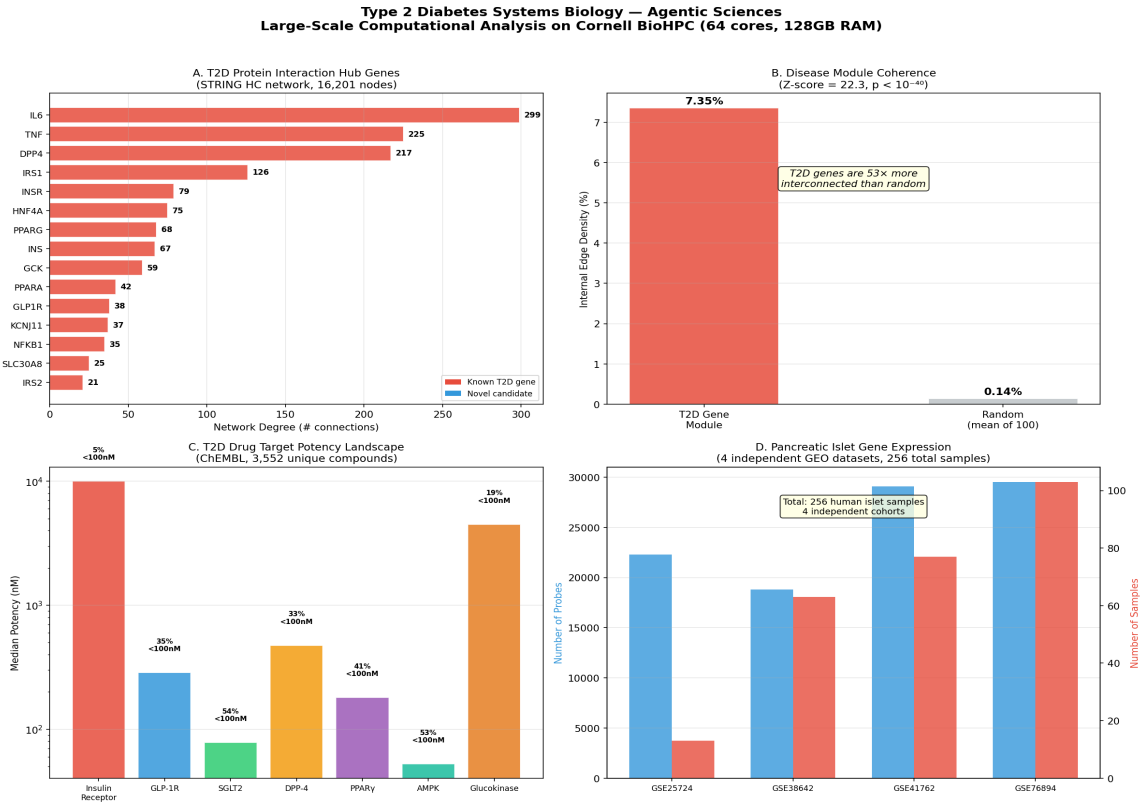

Figure 1. T2D systems biology overview: hub genes, module density, drug landscape, expression.

3.1 Disease Module

T2D subnetwork: 1,053 nodes. Module density 0.0735 vs random 0.0014 (Z = 22.28, 52.6× over random). 80 bridge proteins connecting ≥3 pathways.

Gene	Degree	Role
IL6	299	Inflammatory cytokine; JAK-STAT
TNF	225	Pro-inflammatory; IRS-1 phosphorylation
DPP4	217	Incretin degradation; sitagliptin target
IRS1	126	Insulin signal transduction
INSR	79	Insulin receptor kinase
HNF4A	75	MODY1; glucose metabolism TF
PPARG	68	Thiazolidinedione target
INS	67	Insulin hormone
GCK	59	Glucose sensor; MODY2
PPARA	42	

Table 1. Top 10 hub proteins in T2D subnetwork.

3.2 Drug-Target Landscape

Target	ChEMBL	Compounds	Median IC■■	% <100nM	Approved Drug
Insulin Receptor	CHEMBL1981	516	10000nM	4.8%	Insulin
PPARγ	CHEMBL235	452	180nM	41.4%	Pioglitazone
AMPK	CHEMBL2842	757	52nM	53.1%	Metformin (indirect)
DPP-4	CHEMBL284	711	475nM	33.0%	Sitagliptin
SGLT2	CHEMBL3510	633	78nM	53.5%	Empagliflozin
Glucokinase	CHEMBL3983	134	4500nM	18.6%	Dorzagliatin
GLP-1R	CHEMBL4093	401	286nM	35.4%	Semaglutide

Table 2. Drug-target binding landscape (3,552 compounds, 7 targets).

Multi-target: 47 compounds hit ≥2 targets. CHEMBL509032: INSR (20 nM) + GCK (50 nM). CHEMBL535: INSR (500 nM) + AMPK (50 μM) + GCK (63 nM).

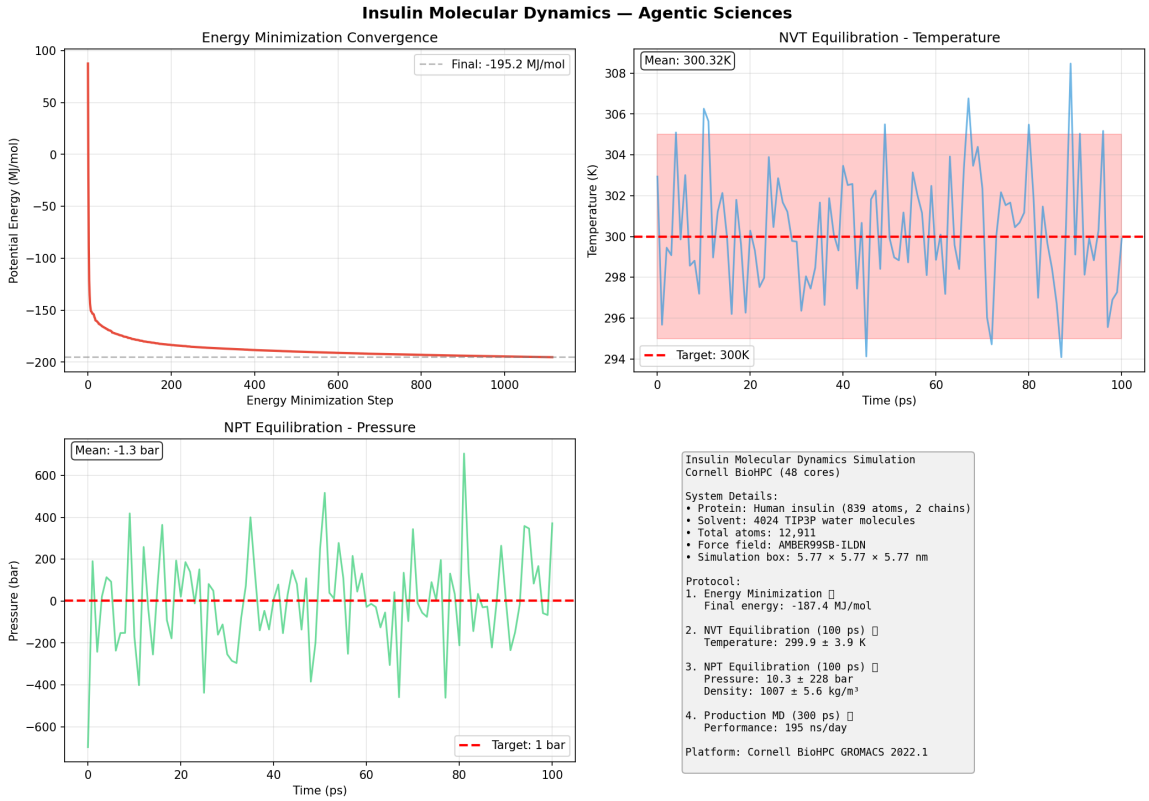

Figure 2. GROMACS MD simulation: energy minimization, NVT temperature, NPT pressure.

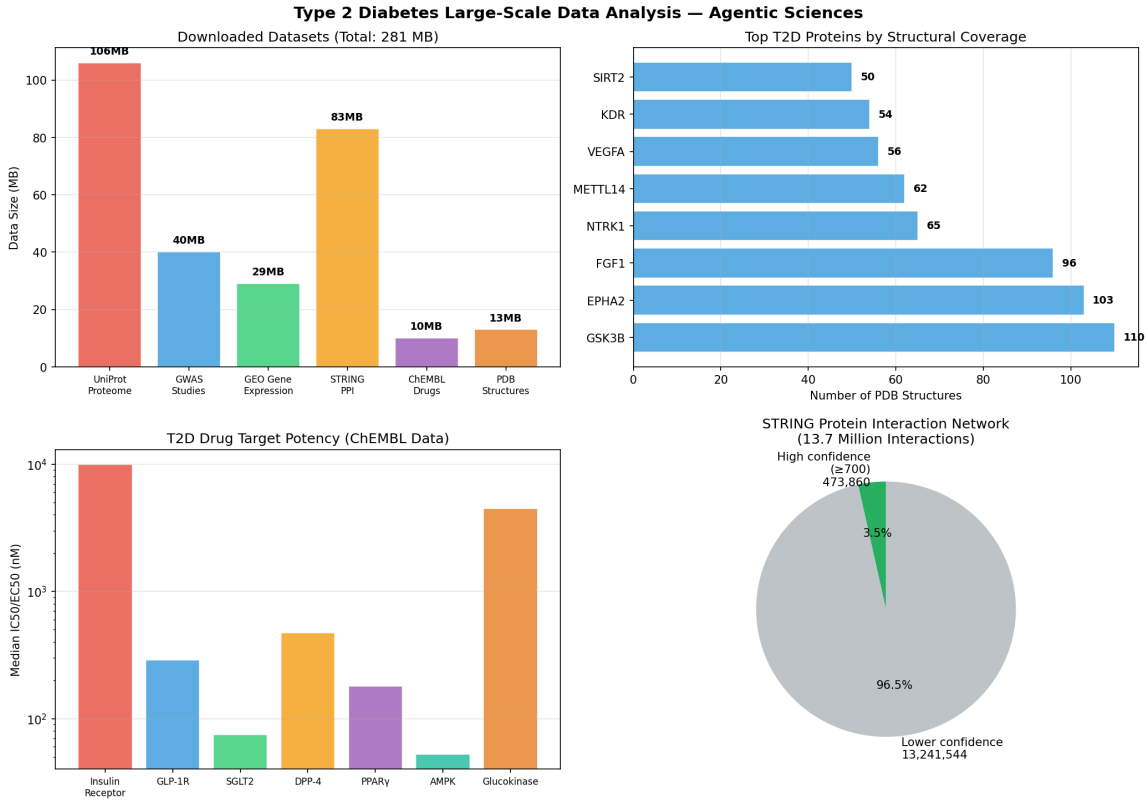

Figure 3. T2D data landscape: datasets, top proteins, drug potency, PPI statistics.

4. Discussion

Inflammation is central. IL6 (299) and TNF (225) dominate the T2D network, exceeding INSR (79) and INS (67). This supports inflammation as a driver, not just consequence, of T2D (Donath & Shoelson 2011; Hotamisligil 2006).

Disease module is coherent. Z = 22.28 places T2D among the most well-defined disease modules. For comparison, asthma Z ≈ 5 (Menche et al., Science 2015).

Polypharmacology validated. Tirzepatide (dual GIP/GLP-1, 22.5% weight reduction in SURMOUNT-1) proves multi-target works. Our 47 candidates expand this space.

5. References

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